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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/056,343	04/07/98	LOEVBORG	U 3556.224-US

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/056,343	Applicant(s) Loevborg
	Examiner William W. Moore	Group Art Unit 1652

☒ Responsive to communication(s) filed on *Oct 27, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *24-39* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *24-39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicants' request for the filing of a Continued Prosecution Application, Paper No. 9, was filed on October 27, 1999. In Paper No. 7 filed February 9, 1999, Applicants elected for prosecution species A, a method of producing industrial and process enzymes described in claims 25-29, as well as variant products of claims 33-34. The restriction requirement was then rescinded and claims 24-34 were examined on the merits in Paper No. 8 mailed April 26, 1999. No amendment or other submission accompanied Paper No. 9 responsive to the rejections and objections of record, and to the indications of informalities, stated in Paper No. 8, thus the contents of Paper No. 8 are restated herein, but this communication is not made final. As noted in Paper No. 8, the application lacks an abstract of the disclosure as required by 37 CFR 1.72(b) and an abstract on a separate sheet is still required.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 24-28 and 32-34 are for reasons of record rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 5,766,898. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 24-28 and 32-34 herein have a scope embracing the subject matter of claims 1-18 of the issued patent.

Claims 24-29 and 32-34 are for reasons of record rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for a method practiced with a polypeptide having a known amino acid sequence, and for a variant product of a native peptide having a known amino acid sequence wherein a native epitope is identified

and changed, does not reasonably provide enablement for methods practiced with a polypeptide the amino acid sequence of which is unknown or for a variant product of a polypeptide the native amino acid sequence of which is unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A determination that distinct epitopes, distinguishable from other epitopes, reside on the surface of a native polypeptide requires no knowledge of the structure(s) that form an individual epitope because a monoclonal antibody raised to the purified, polypeptide may detect on among them, but the claimed method is not a method that may be practiced blindly. This is because no method of changing the amino acid composition of the surface and internal features that form an individual epitope can be practiced unless the primary structure of the polypeptide - its amino acid sequence - is first determined. A claimed method that includes prediction of an epitope, and all of the methods for predicting epitopes practiced in the prior art made of record herewith, requires that the amino acid sequence of a polypeptide be determined. The degree of experimentation required to randomly prepare polypeptide having altered epitopes *de novo* by solid-phase peptide synthesis is deemed to be undue because the amino acid sequence of a polypeptide must be known to attempt to do so and the mere availability of a monoclonal antibody provides no indication of the area or length of a native epitope, its amino acid composition and order of amino acids therein, or whether other features within the primary structure of the polypeptide than a single sequence of amino acids contribute to its presence.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying "Forman" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to enablement). The standard set by the CCPA, the predecessor tribunal of the Court of Appeals for the

Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope of guidance provided by the specification and the scope asserted in the claimed subject matter. *In re Fisher*, 427 F. 2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone). See also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). Given the lack of any guidance in the specification, and in prior art, for determining the composition and size of an epitope without first determining the amino acid sequence of the polypeptide, the absence of any working examples wherein an epitope of a polypeptide is altered without knowledge of its amino acid sequence, the absence of support in the state of the art and level of skill in the art for such alteration as evidenced by the publications of record herein, and the unpredictability in the art that, until the present day, requires foreknowledge of the amino acid sequence of polypeptide in order to define and alter an epitope, the scope of the claimed subject matter embraced by claims 24-29 and 32-34 is not supported by the present specification and limitation of the subject matters as indicated in the statement at page 3 hereinabove is required to overcome this rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35 U.S.C. §103(a).

Claims 24 and 32 are for reasons of record rejected under 35 U.S.C. §102(b) as being clearly anticipated by Luo et al., 1988, **Virology**, Vol. 163, pages 341-348, of record.

Luo et al. disclose the mapping of protein epitopes with an immunological method, monoclonal antibody recognition, and a proteochemical method, protease digestions, and the subsequent determination of the epitopes, as well as identification within recombinantly synthesized DNA molecules of nucleotide changes that produced amino acid changes resulting in, p. 343 and Table 1 at page 344, "at least 60-75% reduction in antigenicity" in three different protein variants.

Claims 24 and 32 are for reasons of record rejected under 35 U.S.C. §102(b) as being clearly anticipated by Keil et al., 1989, **Virology**, Vol. 170, pages 392-407, of record.

Keil et al. disclose the mapping of protein epitopes with an immunological method, monoclonal antibody recognition, informed by a proteochemical analysis, protease foot-printing, and the subsequent determination of the sites of several epitopes in the protein, as well as the preparation by recombinant DNA synthesis of nucleotide changes in DNA molecules encoding the protein: deletions that produced internally truncated variants of the protein. Keil et al. disclose that these deletions resulted in, see Figure 7 and variant products designated vWK3, vWK13 and vWK16, a complete loss of some epitopes reduction and a reduction in antigenicity of others.

Claims 24 and 32 are r for reasons of record ejected under 35 U.S.C. §102(b) as being clearly anticipated by Choo et al., 1988, **Human Immunology**, Vol. 21, pages 209-219, of record.

Choo et al. disclose identification of a protein epitope by an immunological method, monoclonal antibody recognition, and a proteochemical analysis, isoelectric focussing gel electrophoresis, and the subsequent determination of its site in the protein by preparing recombinant DNA molecules encoding either the native protein or a variant protein wherein the variant had reduced antigenicity due to a nucleotide change in the DNA sequence resulting in, p. 213, "only a single amino acid difference at position 59" in one of the four domains of the protein "when compared to the prototype", or native, protein.

Claims 25-27, 30, 31, 33-35 and 39 are for reasons of record rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al., as applied to claims 24 and 32 above, in view of Baxter et al., U.S. Patent No. 5,258,287, Greenfield et al., U.S. Patent No. 4,894,443, Hopp et al., 1981, **Proceedings of the National Academy of Sciences, U.S.A.**, Vol. 78, pages 3824-3828, Zachariae et al., 1981, **Allergy**, Vol. 36, pages 513-516, and Favre et al., 1989, **Molecular Immunology**, Vol. 26, pages 17-25, all of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before. Discussing alteration of the amino acid sequence of a medically-significant human polypeptide which binds the peptide hormone, insulin-like growth factor, Baxter et al. teach, col. 7, lines 1-66, that "[s]ubstantial changes in . . . immunological identity are made by selecting [amino acid] substitutions [introduced as codon substitutions in the underlying DNA sequence] that are less conservative than those in Table 1", and, while "[m]ost deletions and insertions, and substitutions in particular are not expected to produce radical changes in the characteristics of the [native] polypeptide molecule", any uncertainty about "the exact effect of the [chosen] substitution, deletion or insertion . . . when modifying . . . an immune epitope . . . will be evaluated by routine screening assays". Baxter et al. specifically teaches, id. at lines 61-64, that "a change in the immunological character of the [native polypeptide], such as affinity for a given antibody, is measured by a competitive-type immunoassay". While Baxter et al. are concerned with a particular polypeptide that is not an enzyme, Greenfield et al. teach, cols. 7-8, that

native epitopes present in the microbial- or plant-derived enzyme portion of an antibody-enzyme conjugate may identified and "remove[d] . . . by partial proteolytic digestion or by chemical modification" as well as "by cloning and expressing the gene encoding its amino acid sequence" wherein "the epitopes [in the product of genetic engineering] may be removed at the DNA level by recombinant DNA techniques".

Hopp et al. generally teach a series of factors useful in the computer analysis of amino acid sequences in order to predict the antigenic determinants - epitopes - of proteins when provided only the knowledge of their amino acid sequence. Hopp et al. teach, Table 4, their predictions of the primary epitopes in 18 prominent polypeptides of immunogenic significance, including three human interferons. Hopp et al. teach their conclusion, page 3827, of results of an experiment in which the immunogenicity of the first epitope indicated in Table 4 was altered by chemical synthesis of a peptide region comprising the hexapeptide wherein the side chains, residues, of amino acids flanking the hexapeptide were chemically altered to shield their hydrophilic nature, bringing about a failure of antibodies specific for the native peptide region to bind it. Favre et al. teach that a polypeptide, gamma-interferon, used in medical therapy can present epitopes which give rise to antibodies limiting its effectiveness, and map several such epitopes with monoclonal antibodies. Zachariae et al. teach that production of a microbial enzyme having wide industrial applications and a known amino acid sequence, a microbial protease purified from a *Bacillus* species used in formulating detergents, presents health problems for persons exposed to it because their immune systems became sensitized to the purified protease, whereby further exposure to it produced allergic reactions in a significant number of such persons.

In view of the successes in identifying and altering the immunogenicity of specific epitopes in polypeptides disclosed by Choo et al., Keil et al., or Luo et al, as well as the teachings of Baxter et al. and Greenfield et al. of general approaches for reducing the

immunogenicity of medically significant polypeptides and enzymes, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Hopp et al. and of Favre et al. of identification of interferon epitopes by means, respectively, of computer analysis of amino acid sequences and monoclonal antibody mapping, to identify epitopes in the amino acid sequence of a medicinal protein such as a gamma-interferon, and to then alter those sequences, by altering the underlying DNA sequence according to teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes. This is because Favre et al. teach that epitopes present on interferons may limit their medicinal use, because Hopp et al. teach how to identify the antigenic epitopes in a given interferon, native amino acid sequence, and because Baxter et al. and Greenfield et al. teach how to alter or reduce the immunogenicity of epitopes, once identified, by non-conservatively altering the known amino acid sequence of an enzyme or of a medically significant polypeptide by altering the codons of the DNA sequence that encodes it.

It would also have been obvious to one of ordinary skill in the art in view of the teaching of Zachariae et al. of an industrial enzyme, a protease, that presents a health problem to persons handling it to identify epitopes in the amino acid sequence of an industrial protease utilizing the teachings of Hopp et al. and to then alter the amino acid sequences by altering the underlying DNA sequence according to teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes. This is because Zachariae et al. point out the need to solve the problem of immunogenicity of the native protease, because Hopp et al. teach how to identify the antigenic epitopes in a given, native amino acid sequence, because Baxter et al. and Greenfield et al. teach how to alter or reduce the immunogenicity of epitopes in proteins, once identified, by non-conservatively altering the known amino acid sequence of an enzyme by altering the codons of the DNA sequence that encodes it, and because of the successes in identifying

and altering the immunogenicity of specific epitopes in polypeptides disclosed by any of Choo et al., Keil et al., or Luo et al.

Claim 36 is for reasons of record rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al. in view of Baxter et al.('287), Greenfield et al.('443), and Hopp et al., as applied to claims 24, 32 and 35 above, and further in view of Ruttenberg, U. S. Patent 3,903,068, of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before, as are the further teachings of Baxter et al., Greenfield et al., and Hopp et al. Ruttenberg generally teaches that chemical and enzymatic treatment of porcine insulin will convert its amino acid sequence which presents an epitope immunogenic in humans into the amino acid sequence of human insulin, abolishing its immunogenicity. In view of the successes of any among Choo et al., Keil et al., or Luo et al, in identifying and altering the immunogenicity of specific epitopes in polypeptides, as well as the teachings of Baxter et al. and Greenfield et al. of general approaches for reducing the immunogenicity of polypeptides and enzymes and the further teaching of Hopp et al. of identifying epitopes when the amino acid sequence of the polypeptide is known, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use recombinant DNA technology as taught by Baxter et al. and Greenfield et al. to change the amino acid sequence of an insulin produced by one mammalian species to the amino acid sequence of an insulin of a mammalian species in which its medicinal use is desired, such as human insulin, to remove an epitope that can raise an unwanted immune response in the desired species, as Ruttenberg had laboriously done, since recombinant expression of a genetically altered, immunogenic epitope-free, insulin would clearly be economically advantageous.

Claims 37 and 38 are for reasons of record rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al. in view of Baxter et al.('287), Greenfield et al.('443), and Hopp et al., as applied to claims 24, 30, 32 and 35 above, and further in view of Fulton et al., U. S. Patent No. 4,970,300, of record,

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before, as are the further teachings of Baxter et al., Greenfield et al., and Hopp et al. Fulton et al. generally teach that chemical treatment of purified human Factor VIII permits the conjugation thereto of non-antigenic polymers in order to reduce, col. 2 at lines 48-56, the production of inhibitory antibodies raised by infusion of human Factor VIII to treat clotting disorders in as many as 14% of patients receiving such treatment. Fulton et al. also teach, col. 2 at lines 3-7, that the Factor VIII gene had been cloned permitting recombinant production of human Factor VIII. In view of the successes of any among Choo et al., Keil et al., or Luo et al, in identifying and altering the immunogenicity of specific epitopes in polypeptides, as well as the teachings of Baxter et al. and Greenfield et al. of general approaches for reducing the immunogenicity of polypeptides and enzymes and the further teaching of Hopp et al. of identifying epitopes when the amino acid sequence of the polypeptide is known, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the amino acid sequence of Factor VIII from the cloned gene and scan that amino acid sequence with the computer analysis taught by Hopp et al. in order to identify the potential epitopes that contribute to the formation of anti-Factor VIII antibodies in as many as 14% of the patients who receive it in infusions to treat clotting disorders in order to apply the teaching of Baxter et al. of recombinant DNA technology in changing the amino acid sequence of each potential epitope in turn to reduce the immunogenicity of native Factor VIII in its desired medicinal use as a clotting enzyme.

Claims 28, 29 and 34 are for reasons of record rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Choo et al., Keil et al., or Luo et al. in view of Baxter et al.('287), Greenfield et al.('443), Hopp et al. and Zachariae et al. as applied to claims 24, 25, 32 and 33 above, and further in view of Nielsen et al., U. S. Patent No. 4,560,651, of record.

The disclosures of Choo et al., Keil et al., or Luo et al., discussed hereinabove, are taken as before, as are the further teachings of Baxter et al., Greenfield et al., and Hopp

et al. Nielsen et al. generally teach the purification of an enzyme, an amylase, from a *Bacillus* species in order to use it in processes for treating starches to convert them to syrups and also teach that the amylase is likely, cols. 5-6, to be sufficiently immunogenic in mammals to permit production of antibodies that will recognize its particular epitopes and allow industrial process users of the amylase to distinguish it from amylases produced by other strains of the same *Bacillus* species as well as to distinguish it from other microbial amylases. In view of the teaching of Zachariae et al. that an enzyme that must be purified from a microbial source, a *Bacillus* species, for further applications in industrial can present a health problem to persons handling it by sensitizing their immune systems, and also in view of the successes of any of Choo et al., Keil et al., or Luo et al, in identifying and altering the immunogenicity of specific epitopes in polypeptides, it would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the amino acid sequence of the amylase by standard procedures in the art and to utilize the teachings of Hopp et al. to identify epitopes in its amino acid sequence and to then alter the amino acid sequences by altering any isocoding DNA sequence that may be synthesized to specify that amino acid sequence according to teachings of Baxter et al. and Greenfield et al., to abolish or diminish the immunogenicity of those epitopes. This is because such an artisan at that time could reasonably expect that the enzymes originally produced by microbes will be immunogenic to persons regularly exposed to them and that the amylase purified by Nielsen et al. would be placed in commercial production for use in starch processing, thus exposing persons to it in purified form. This is because such an artisan at that time could reasonably expect that determining the amino acid sequence of the amylase would permit identification of its potential epitopes by the method of Hopp et al. and that suitable changes in the amino acid sequence would be produced by application of the teachings of Baxter et al. and Greenfield et al., to abolish or diminish

the immunogenicity of those epitopes by changing the appropriate codons in a synthetic gene designed to specify the native amylase amino acid sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is (703) 308-0583. The examiner can be reached Monday through Friday from 9:00 AM to 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published November 15, 1989 in the Official Gazette, 1096 OG 30. Informal and unofficial communications may be sent to the Art Unit 1652 FAX number, (703) 308-0294. Official filings should be sent to the Technical Center 1600 FAX number which is (703) 308-4556.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. §122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark Office on February 25, 1997 at 1195 OG 89. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

William W. Moore
December 13, 1999

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